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Effect of propranolol on the QT intervals of normal individuals during exercise: a new method for studying interventions

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SUMMARY A new method was used to study the effect of a single dose of propranolol on the QT intervals during exercise in 11 normal volunteers. They exercised maximally on a bicycle ergometer and repeated the test after taking propranolol (40 mg) by mouth two hours before. Electrocardiograms were continuously recorded on magnetic tape and the cardiac cycle length (RR interval) and the QT interval were measured every five seconds by a computer aided method. The RR-QT data from each test during the exercise phase were analysed by an exponential formula, $QT = A - B \times \exp(-k \times RR)$ and by Bazett's formula, $QT = K \times \sqrt{(RR)}$. Three reference QT intervals, QT_{c1}, QT_{c2}, and QT_{c3}, estimated at RR = 400, 700, and 1000 ms respectively from the regression curves of both formulas were compared. The exponential formula, which consistently gave a better fit with the data, showed that propranolol had a biphasic action on the QT intervals during exercise. It significantly prolonged the mean (SD) interval at longer cycle lengths (from 287 (27) to 305 (18) ms at RR = 1000 ms and shortened it at shorter cycle lengths (from 198 (14) to 179 (16) ms at RR = 400 ms). In contrast, Bazett's formula did not show any significant effect when the same raw data were used.

The exponential formula can be adapted to study other interventions or conditions that affect QT intervals.

The results of previous studies of the effect of propranolol on the QT interval are contradictory. Milne *et al* showed that intravenous propranolol prolonged the QT interval at identical atrial paced cycle lengths,[1] whereas Browne *et al* found no significant changes under similar conditions[2]; however, the use of Bazett's formula[3 4] shortened the rate corrected QT interval calculated from both studies. Other studies of propranolol also suggested that the QT interval corrected for heart rate by Bazett's formula was usually shortened.[5 6]

We found that the functional dependence of the human QT interval on the cardiac cycle length (RR interval) during exercise and cardiac pacing was well expressed by an exponential formula.[7] We used this exponential formula to evaluate the effects of propranolol on the QT intervals of normal individuals during exercise and we compared the results with an analysis of the same data by Bazett's formula.

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Patients and methods

Eleven healthy volunteers (six men and five women, mean (SD) age 34 (7) years (range 20–48)) exercised maximally on a bicycle ergometer. They exercised once without medication after an overnight fast, and seven to 10 days later they exercised again after taking 40 mg of propranolol by mouth two to three hours before the test. This dose slowed the heart rate and caused visible symptoms of tiredness in all the volunteers, none of whom had taken propranolol before. For each test, the initial exercise load was set at 50 W and was increased in steps of 25 W every two minutes. Electrocardiographic leads I, aVF, and V5 were continuously recorded on an analogue tape recorder (Model HP3964A, Hewlett-Packard, Palo

Alto, CA) that was started three minutes before exercise. This study protocol was approved by our institutional review board. Each person signed a form giving informed consent.

The RR and QT intervals were measured automatically every five seconds by a programmable waveform analyser (Model 3001, Norland, Fort Atkinson, WI) and the data were transmitted to an IBM-PC/AT microcomputer (IBM Personal Computer Division, Boca Raton, FL) over an IEEE-488 interface. The QT interval was measured from the beginning of the QRS complex to the apex of the T wave. In eight people in whom the end of the T wave could be clearly identified throughout the exercise the average interval from apex T to end T (eT-aT interval) was measured at rest and peak exercise. The end of the T wave was taken as the point at which the line drawn through the steepest portion of the terminal limb of the T wave cut the isoelectric line defined by the PQ segment.[8]

The RR-QT data during the exercise phase were fitted to the exponential formula[7]: $QT = A - B \times \exp(-k \times RR)$, where the parameters A, B, and k were estimated by non-linear regression with the *ASYST* scientific system (Macmillan Software, New York, NY). For comparison, the exercise RR-QT plots were also fitted to Bazett's formula[3]: $QT = K \times \sqrt{(RR)}$, in which the parameter K was estimated by linear regression. The measurements made during the recovery phase were not included in the analysis, to avoid the effects caused by QT hysteresis.[8]

DATA ANALYSIS

We compared the three reference QT intervals, QT_{c1}, QT_{c2}, and QT_{c3}, estimated from the individual regression curves at RR = 400, 700, and 1000 ms, respectively, in the control and propranolol groups. These estimates may be regarded as corrected QT intervals (see the Appendix). They are expressed as functions of the regression equations as follows:

$$QT_{c1} = A - B \times \mathrm{Exp}(-k \times 400)$$
$$QT_{c2} = A - B \times \mathrm{Exp}(-k \times 700)$$
$$QT_{c3} = A - B \times \mathrm{Exp}(-k \times 1000),$$

where the QT_c intervals are expressed in ms. A set of three QT_c intervals are required to characterise uniquely each exponential RR-QT curve. We chose the corrected QT intervals for statistical comparisons because this permits the drug induced changes in the QT_c estimates to be interpreted in terms of prolongation or shortening of QT intervals in the observable range of cycle lengths. Similar estimates of the QT_cs derived from Bazett's (or any other) formula can be compared with the values derived from the exponential formula.

The corrected QT intervals at RR = 400, 700, and 1000 ms according to Bazett's formula were estimated by the following equations:

$$QT_{c1} = K \times \sqrt{(400)}$$
$$QT_{c2} = K \times \sqrt{(700)}$$
$$QT_{c3} = K \times \sqrt{(1000)},$$

where the QT_c intervals are also expressed in ms. QT_{c3} corresponds to the conventional corrected QT interval. Zipes recently suggested that when the effects of drugs or other interventions are being evaluated the original Bazett's formula, $QT = K \times \sqrt{(RR)}$, where the K value is derived from a regression analysis, is superior to the commonly applied formula, $QT_c = QT/\sqrt{(RR)}$.[9] The relation between the two formulas is explained in the Appendix.

We compared matched sets of control and propranolol treatment values of QT_{c1}, QT_{c2}, and QT_{c3} by the one sample Hotelling T^2 test for overall differences and differences among individual pairs of QT_cs by a paired *t* test. We used the same method to analyse the corrected QT intervals obtained by Bazett's formula. *BMDP Statistical Software* (Los Angeles, CA) was used for the statistical analysis.

Results

Table 1 summarises the main results. Cardiac cycle lengths at rest and peak exercise were significantly prolonged after propranolol. Systolic blood pressure at rest and peak exercise was significantly reduced. There were no pronounced changes in diastolic blood pressures. As expected, none of the subjects showed any abnormalities during exercise or recovery. The QRS configuration was unchanged during exercise and between tests. The QRS duration remained less than 5 ms throughout the study. The average duration of exercise was not signifi-

Table 1 *Summary of results (mean (SD)) obtained from 11 volunteers who exercised under control conditions and after propranolol*

Measured variable	*Control*		*Propranolol*		*p (pair)*
CCL resting (ms)	869	(151)	1174	(168)	<0·001
CCL peak exercise (ms)	334	(23)	444	(44)	<0·001
Systolic BP resting (mm Hg)	106	(11)	99	(11)	<0·05
Diastolic BP resting (mm Hg)	70	(7)	68	(9)	NS
Systolic BP peak (mm Hg)	159	(19)	141	(24)	<0·01
Diastolic BP peak (mm Hg)	75	(12)	75	(11)	NS
Exercise duration (min)	11·1	(2·5)	10·3	(2·7)	NS
QT_{c1} (exponential) (ms)	198	(14)	179	(16)	<0·002
QT_{c2} (exponential) (ms)	257	(16)	271	(17)	<0·001
QT_{c3} (exponential) (ms)	287	(27)	305	(18)	<0·01
QT_{c1} (Bazett) (ms)	196	(13)	198	(13)	NS
QT_{c2} (Bazett) (ms)	259	(17)	261	(17)	NS
QT_{c3} (Bazett) (ms)	309	(20)	312	(20)	NS

BP, blood pressure; CCL, cardiac cycle length.

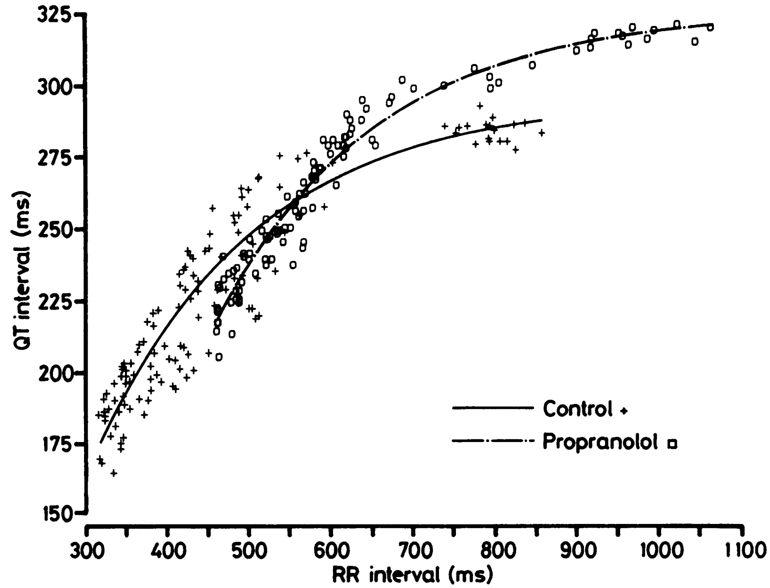

Fig 1 *A typical plot showing the RR-QT relation during exercise before (+) and after (○) propranolol together with the fit of the regression line with the exponential formula. The apparent gap in the data points on the control curve represents a rapid shortening of cycle length during the early part of exercise. Propranolol typically caused more gradual RR shortening, resulting in a more uniform distribution of data points.*

cantly altered by propranolol treatment, although all the volunteers found it harder to exercise after taking the drug.

Figure 1 shows typical plots of RR versus QT and their regression lines obtained with and without propranolol treatment in one volunteer.

Table 1 shows that there were significant differences between the control and treatment values for corrected QT intervals obtained with the exponential formula (QT_{c1}, QT_{c2}, QT_{c3}) ($p < 0{\cdot}002$, Hotelling T^2 test); after propranolol QT_{c1} was significantly shortened and QT_{c2} and QT_{c3} were significantly prolonged. Figure 2 shows the QT_c changes in individual volunteers. In contrast with the exponential formula, the corrected QT intervals obtained with Bazett's formula failed to show any significant difference between the control and treatment values (table 1), although the same raw data were used in both calculations. Figure 3 compares the curves obtained with the exponential and Bazett's formulas for the exercise data used in fig 1. The exponential formula gave a consistently better fit with the observed data.

The changes in the T wave configuration during exercise were similar under control conditions and after propranolol treatment. The average (SD) eT-aT intervals measured in eight volunteers at rest were 149 (17) ms for control and 145 (14) ms after propranolol (p = NS). The values at peak exercise were 124 (22) for control and 125 (15) after propranolol (p = NS). Thus the Q-aT and Q-eT intervals showed parallel behaviour in this study.

To assess whether the RR-QT relation is dependent on the exercise protocol, we studied a separate group of five normal volunteers (three men, two women; age 22 (5)) who exercised maximally on a bicycle ergometer (50 W initial load with 25 W increases every two minutes) and a treadmill (Bruce protocol) on different days in a random order. The results (table 2) show that the RR-QT relation during the exercise phase is highly reproducible and independent of the exercise protocol.

Discussion

The present study evaluated the effects of a single oral dose of propranolol (40 mg) on the RR-QT relation in normal individuals. The effects on resting and exercise heart rate and blood pressure showed evidence of β blockade, albeit incomplete. Under these conditions the results presented in this report clearly show a biphasic effect of propranolol on the

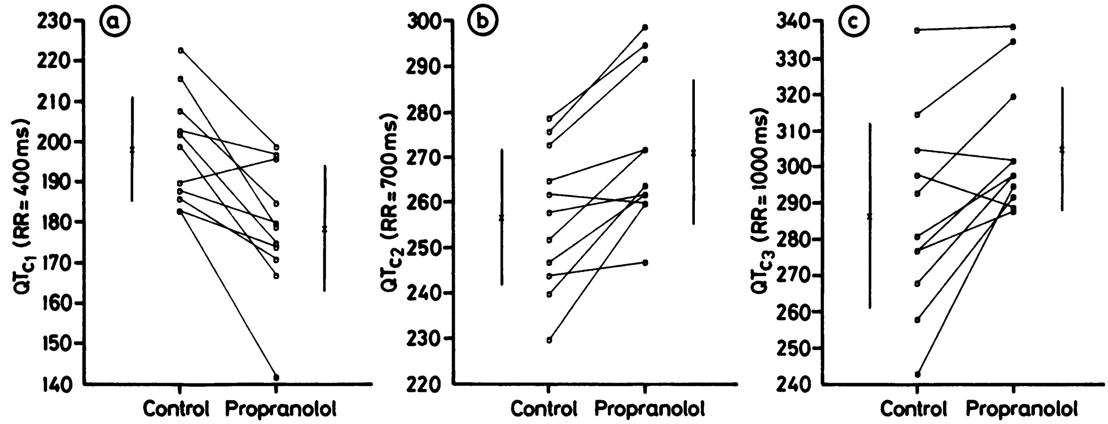

Fig 2 *Effect of propranolol on the individual (a) QT_{c1} intervals estimated at RR = 400 ms, (b) QT_{c2} intervals estimated at RR = 700 ms, and (c) QT_{c3} intervals estimated at RR = 1000 ms. The mean (SD) values for each group are shown. Propranolol had a biphasic effect, shortening QT_{c1} ($p < 0{\cdot}002$) but prolonging QT_{c2} ($p < 0{\cdot}001$) and QT_{c3} ($p < 0{\cdot}01$).*

exercise QT intervals, with net prolongation at rest and shortening at peak exercise. The high reproducibility of the exercise RR-QT curves and their apparent independence of the exercise protocol indicate the reliability of the results. Milne *et al* found that propranolol causes a uniform QT prolongation over a wide range of identical paced cycle lengths.[1] This finding, taken together with the present results, suggests that a normal tendency of propranolol to prolong the QT interval is opposed by a competing mechanism during exercise. Others have shown that pretreatment of normal individuals with propranolol increases their peak concentrations of plasma potassium and catecholamine during exercise.[10-13] It was suggested that β_2 receptor mediated effects in the exercising muscles may cause the observed hyperkalaemia. An increased extracellular potassium concentration, which is known to shorten the action potential duration in the ventricular muscle,[14] might have resulted in the relative shortening of the QT interval at peak exercise.

The measurement of QT interval to the apex of the T wave rather than to its end is justified in the present study because the changes in the T wave configuration during exercise did not contribute to the differences between the control and propranolol treated conditions. Under these conditions it is better to use the Q-apexT interval which can be measured more accurately.[15]

Propranolol is used in the treatment of long QT syndrome[16] and is known to increase the otherwise low variability of the QT interval during exercise in those patients.[17] It is interesting to note that propranolol also increases the responsiveness of QT intervals in normal subjects through the biphasic effect.

Though Bazett's formula is simpler to use, it is inappropriate for the study of QT intervals during exercise. Mathematically, two regression curves constructed by Bazett's formula cannot cross each other, except at the origin, irrespective of the nature of the data sets. Thus it is theoretically impossible to demonstrate the rate dependent biphasic effect of propranolol on the exercise QT interval by Bazett's formula (fig 3).

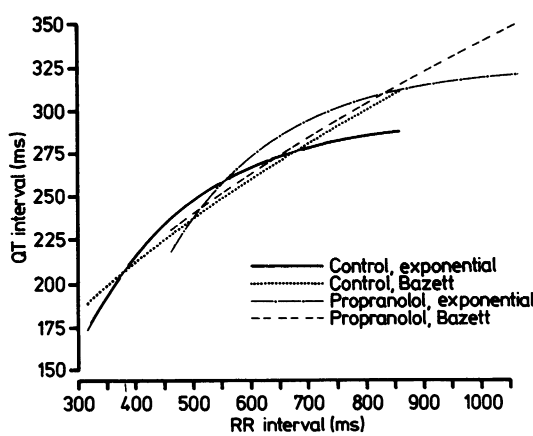

Fig 3 *Comparison of the fit of the exponential and Bazett formulas with the RR-QT data shown in fig 1. The regression curves for Bazett's formula deviated markedly from the data points and showed very little change after propranolol administration. Bazett's curves are mathematically precluded from intersecting except at the origin.*

Table 2 *Reproducibility of QT_c parameters in five normal individuals who exercised on bicycle and treadmill on different days in a random sequence*

No	Exercise type	Exercise duration (min)	QT_{c1} (ms)	QT_{c2} (ms)	QT_{c3} (ms)
1	Bicycle	9·1	197	272	307
	Treadmill	14·0	198	269	309
2	Bicycle	10·0	198	266	304
	Treadmill	13·0	195	263	302
3	Bicycle	10·0	189	256	285
	Treadmill	14·0	192	248	277
4	Bicycle	16·0	199	266	295
	Treadmill	15·0	199	267	299
5	Bicycle	12·0	188	252	281
	Treadmill	13·4	191	257	287
Mean (SD)	Bicycle	11·4 (2·5)	194 (5)	262 (8)	294 (11)
Mean (SD)	Treadmill	13·9 (0·7)	195 (4)	260 (8)	294 (13)
p		NS	NS	NS	NS

QT_{c1}, QT_{c2}, and QT_{c3} were estimated according to the exponential equations given in the text.

IMPLICATIONS

The present study offers a general method for studying the effects of various interventions on the dynamic behaviour of the QT interval. The concept of corrected QT (QT_c) interval has been extended to be applicable to any RR-QT formula. In the case of the exponential formula, QT_c may be regarded as a three dimensional vector with QT_{c1}, QT_{c2}, and QT_{c3} as its components. Other important features of the method include the analysis of individual RR-QT curves without prior pooling, and use of computer aided measurement of time intervals to collect accurately large numbers of data points, all of which contribute to the QT_c estimates. The results presented here offer convincing evidence that the method is sensitive enough to detect subtle, but potentially important, changes in QT intervals caused by interventions. We suggest that this method should be adopted in future investigations, under appropriate conditions.

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Appendix

GENERALISED DEFINITION OF THE CORRECTED QT (QT_C) INTERVAL

To extend the concept of QT_c to formulas other than Bazett's, we first need to define QT_c in general terms as follows:

If the dependence of the QT interval on the cardiac cycle length is represented by the equation

$$QT = f(RR),$$

where f(RR) is a known function of the RR interval, then QT_c is, by definition, given by

$$QT_c = f(RR_r),$$

where RR_r is a reference cycle length chosen such that f(RR) gives consistent results for $RR = RR_r$. For practical reasons RR_r should be chosen within the expected physiological range of RR. It is possible to define more than one QT_c by assigning different values to RR_r. This feature is essential for the multiparameter formulas, as explained later.

APPLICATION TO BAZETT'S FORMULA

Bazett's formula is written as: $QT = K \times \sqrt{(RR)}$. Application of the above definition yields: $QT_c = K \times \sqrt{(RR_r)}$. From these two equations we get:

$$K = \frac{QT_c}{\sqrt{(RR_r)}} = \frac{QT}{\sqrt{(RR)}}.$$

Now, if RR is expressed in seconds and RR_r is set to 1 s, we get the popular equation:

$$QT_c = \frac{QT}{\sqrt{(RR)}},$$

which was first given by Taran and Szylagyi[4] without a clear mathematical explanation. The general definition given above, however, is consistent with the conventional definition of QT_c.

APPLICATION TO THE EXPONENTIAL FORMULA

According to the general definition, the QT_c for the exponential formula is given by:

$$QT_c = A - B \times \exp(-k \times RR_r).$$

Unlike Bazett's formula, however, the exponential formula requires three QT_c values defined at three well spaced RR_r values, to characterise uniquely each exercise curve. These QT_c values may be defined as

$$QT_{ci} = A - B \times \exp(-k \times RR_{ri}),$$

where RR_{ri} = 400, 700, and 1000 ms for i = 1, 2, and 3 respectively. This particular set of RR_{ri} values is suitable for comparing exercise RR-QT curves. The curves can be reconstructed from the above set of QT_{ci} parameters by use of the well known Newton-Raphson recursion algorithm[18] to solve for A, B, and k. Thus QT_{ci} and the model parameters (A, B, k) contain the same information on the RR-QT curves. The former set is preferred, however, because the changes in QT_{ci} are easier to interpret in physiological terms.

In order to use multiparameter formulas, there must be some way to change the RR interval over an appropriate range to obtain reliable estimates of the model parameters. With narrow RR interval ranges, the influence of measurement and rounding errors may render the parameter estimates unreliable. Cardiac pacing and exercise provide non-pharmacological means of producing a sufficiently wide range of RR intervals under fairly controlled conditions. Autonomic tests such as the Valsalva manoeuvre and cold pressor treatment may also be applied, but the RR changes tend to be relatively narrow and therefore higher precision in the RR and QT measurements may be required.

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